HSV

The epidemiology of genital infection with herpes simplex virus types 1 and 2 in genitourinary medicine attendees in inner London

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Objective: To characterise the epidemiological and clinical features of genital herpes and the diagnostic role of HSV-2 specific serology in an ethnically diverse cohort of genitourinary medicine (GUM) attendees in inner London.

Methods: Genital swabs (n = 186) were tested by real time polymerase chain reaction (PCR) and serum samples (n = 70) by HSV-2 specific enzyme linked immunoassay (ELISA).

Results: Among 186 patients (median age 29 years), 104/186 (56%) were male and 176/186 (95%) heterosexual; ethnicity was predominantly black Caribbean (76/186, 41%), white (65/186, 35%), or black-African (41/186, 22%). The most common lesion sites were penis (85/104 men, 82%) and vulva (63/82 women, 77%); 114/186 (61%) patients were diagnosed clinically with first episode disease. Women were more likely to present <5 days of onset ($p = 0.008$). Black Caribbean patients were more likely to present ≥ 5 days ($p = 0.04$) and decline HIV testing ($p = 0.03$). By PCR, 108/186 (58%) swabs tested positive for HSV-1 (7/108, 6.5%) or HSV-2 (101/108, 93.5%). Independent predictors of a positive PCR were heterosexual group, <5 days of onset, and visible genital ulceration on examination. HSV-2 was associated with black Caribbean and black African ethnicity; HSV-1 with white ethnicity ($p = 0.006$). By HSV-2 specific serology, 16/42 (38%) first episodes caused by HSV-2 were recurrent infections, and 7/19 (37%) patients with recurrent genital disease but negative PCR had genital herpes.

Conclusions: Epidemiological trends in genital HSV-1 and HSV-2 infection appear to vary between ethnic groups in the United Kingdom. HSV-2 specific serology improves diagnostic accuracy in GUM populations where most genital infections are caused by HSV-2.

Genital herpes is increasingly common in the United Kingdom.[1] Although the infection has traditionally been associated with herpes simplex virus type 2 (HSV-2), HSV-1 accounts for 22% to 71% of cases in several genitourinary medicine (GUM) populations in England and Scotland.[2] As genital infection with HSV-1 has a relatively mild natural history compared to infection with HSV-2,[3] determining the HSV type provides important information for management and counselling.

In recent years, polymerase chain reaction (PCR) has increased HSV detection rates in genital swabs by up to 71% compared to virus culture.[4] HSV type specific antibody assays with high sensitivity and specificity have also been developed. Using these new diagnostic tools, this study investigated an ethnically diverse cohort of GUM attendees presenting with symptoms suggestive of genital herpes.

METHODS

The clinical diagnosis of genital herpes and of first or recurrent episode was left to the treating physician. HSV was detected and typed in genital swabs by LightCycler PCR (Roche Diagnostics, Germany).[4] HSV type was confirmed by sequencing (n = 14) and by immunofluorescence staining of virus isolates (n = 66) (data not shown). In 70 patients, sera collected for HIV or syphilis screening were labelled as first/recurrent episode and HSV PCR positive/negative, anonymised, and with ethical approval tested retrospectively by ELISA (HerpeSelect HSV-2 ELISA IgG, Focus Technologies, CA, USA). To increase specificity, the cut off was raised from 1 (recommended by the manufacturer) to 3; samples with index values from 0.9 to 3 were scored as equivocal. Four equivocal results were confirmed positive by immunoblot (HerpeSelect Immunoblot IgG, Focus Technologies). Ten samples tested HSV-2 antibody positive at the Health Protection Agency central reference laboratory. Statistical analyses were performed using SAS version 8; χ^2 or Fisher's exact tests were used for qualitative variables, Mann-Whitney U tests for quantitative variables.

RESULTS

Study population

The study comprised 186 consecutive patients (median age 29 years, range 16–67); 104/186 (56%) were male and 176/186 (95%) were heterosexual. The most common lesion sites were the penile skin in men (85/104, 82%) and the vulva in women (63/82, 77%). Other lesion sites were urethra and scrotum in men and vagina and buttocks in women. Women were more likely to present <5 days of the onset of symptoms (51/82, 62% *v* 43/104, 41%; $p = 0.008$). There were no other gender related differences, except that the ten homosexuals were all male.

Table 1 summarises the demographic and clinical data stratified by ethnic group, assigned as described by the UK census categories. Among 76/186 (41%) black Caribbean patients, 39/76 (51%) were from Jamaica and 37/76 (49%) from the United Kingdom. Among 65/186 (35%) white patients, 56/65 (86%) were from the United Kingdom and 9/65 (14%) from other European countries (n = 6) or America (n = 3). Among 41/186 (22%) black African patients, 29/41 (71%) were from sub-Saharan Africa (Zimbabwe, Nigeria,

Abbreviations: GUM, genitourinary medicine; ELISA, enzyme linked immunoassay; HSV, herpes simplex virus; PCR, polymerase chain reaction

Table 1 Demographic and clinical characteristics of patients presenting with suspected genital herpes, stratified by ethnic group*

	Black Caribbean	White	Black African	
	No (%)	No (%)	No (%)	p Value†
Number	76	65	41	
Sex				
Male	41 (54)	35 (54)	24 (59)	
Female	35 (46)	30 (46)	17 (42)	0.87
Sexual orientation				
Heterosexual	76 (100)	56 (86)	41 (100)	
Homosexual	0 (–)	9 (14)	0 (–)	**0.0002**
Age				
Median	28	29	33	**0.03**
Range	16–57	17–61	18–67	
Disease				
First episode	51 (67)	38 (59)	22 (54)	
Recurrent	25 (33)	27 (42)	19 (46)	0.32
Onset				
<5 days	47 (62)	27 (42)	19 (46)	
⩾5 days	29 (38)	38 (59)	22 (54)	**0.04**
Visible ulceration	57 (75)	43 (66)	32 (78)	0.34
HIV status				
Negative	30 (39)	34 (52)	18 (44)	
Positive	6 (8)	4 (6)	9 (22)	
Declined testing	40 (53)	27 (42)	14 (34)	**0.03**

*The four patients with ethnicities other than black Caribbean, white, or black African were excluded.
†p Value obtained from χ^2, Fisher's exact, or Mann-Whitney U tests, as appropriate.

Ghana, Zambia, and Uganda) and 12/41 (29%) from the United Kingdom (n = 11) or France (n = 1). Three patients were from the Indian subcontinent and one from the Middle East. The homosexual men were all white. Black African patients were older than those from other ethnic groups. Patients of white ethnicity were the most likely to present <5 days of onset, whereas black Caribbean patients were the least likely. This emphasises the need to facilitate access to care for groups that are recognised as vulnerable to sexually transmitted infections.[5]

Table 2 Characteristics of patients whose genital swabs tested positive for HSV

	HSV PCR positive*
	No (%)
Sex	
Male	57 (55)
Female	51 (62)
Ethnic group	
Black Caribbean	49 (65)
White	33 (51)
Black African	25 (61)
Other	1 (25)
Sexual orientation	
Heterosexual	106 (60)
Homosexual	2 (20)
Disease	
First episode	62 (54)
Recurrent	46 (64)
Onset	
<5 days	62 (66)
⩾5 days	46 (50)
Ulceration	
No	15 (29)
Yes	93 (69)
HIV status	
Negative	51 (61)
Positive	14 (74)
Declined testing	43 (52)
Age	
Those with negative PCR	29 (16–54)
Those with positive PCR	30 (17–67)

*HSV positive results included both HSV-1 and HSV-2 positive swabs.

HIV testing was declined by 83/186 (45%) patients. Among the 103 patients tested, HIV status was positive in 9/27 (33%) black African, 4/38 (11%) white, and 6/36 (17%) black Caribbean patients. Black Caribbean patients were more likely to decline HIV testing compared to other ethnic groups. This agrees with findings from the UK Unlinked Anonymous Prevalence Monitoring Programme indicating that between 1997 and 2001, of those born in the Caribbean 50–73% left the GUM clinic unaware of their HIV infection.[6] Estimated HIV infection rates are significant in this group, ranging from 0.6–0.7% among heterosexuals to over 10% among male homosexuals.[6]

HSV detection in genital swabs

HSV was detected in 108/186 (58%) swabs (table 2); 101/108 (93.5%) infections were caused by HSV-2. The proportion of HSV-1 positive swabs was 4/58 (7%) in men and 3/51 (6%) in women, and 5/62 (8%) in first episodes and 2/46 (4%) in recurrent episodes. In multivariate analysis, homosexual risk group was an independent predictor of a negative HSV PCR (odds ratio, OR 0.16; 95% confidence interval, CI 0.03 to 0.83; p = 0.03) Independent predictors of a positive HSV PCR were <5 days of onset (OR 2.00; 95% CI 1.04 to 3.81; p = 0.04) and presence of visible genital ulceration (OR 5.63; 95% CI 2.73 to 11.61; p = 0.0001). Thus, even when using PCR the diagnosis of genital herpes remains significantly dependent on a timely presentation. There were no significant differences in the rate of HSV detection between men and women, between first and recurrent episodes, and according to HIV status. Analysis by ethnic origin showed that a similar proportion in each group tested positive for HSV. Among those who tested HSV positive, however, HSV-1 was significantly more common in white patients (5/33 HSV positive samples, 15%) while HSV-2 was more common in black African and black Caribbean patients (73/74 HSV positive samples, 99%) (p = 0.006).

HSV-2 specific serology

The study investigated the potential diagnostic contribution of HSV type specific serology. In published prospective studies of newly acquired genital herpes, the median time to the development of HSV-2 antibodies from the onset of symptoms was 21–23 days, as determined by the HerpeSelect

HSV-2 ELISA.[7] In this study, among patients with a history of recurrent genital herpes and HSV-2 positive PCR, 9/9 (100%) had HSV-2 antibodies at the time of presentation, consistent with the clinical diagnosis. Among patients with first episode genital disease and HSV-2 positive PCR, 26/42 (62%) lacked HSV-2 antibodies, consistent with a newly acquired infection; the remaining 16/42 (38%) had HSV-2 antibodies at the time of presentation, indicating that the infection was established.[8] These findings confirm that even with experienced clinicians, differentiating between newly acquired and recurrent infections can be difficult on the basis of clinical history alone. One limitation was that antibody testing was anonymised and therefore no follow up was possible to demonstrate seroconversion in newly acquired infections. Among patients with a history of recurrent genital disease but negative HSV PCR, 7/19 (37%) had HSV-2 antibodies, indicating that genital herpes was the likely cause of the recurrent symptoms.

DISCUSSION

In contrast with findings from several other GUM clinics in the United Kingdom, HSV-2 was the most prevalent cause of genital herpes in this ethnically diverse population. A significant association was found between black ethnicity and HSV-2 infection. To explain this observation, one could speculate that black Caribbean and black African patients were less likely than patients of white ethnicity to attend the GUM clinic if infected with HSV-1. None the less, it is plausible that the high rates of oropharyngeal HSV-1 acquisition during childhood observed both in people of black ethnicity and in socioeconomically disadvantaged populations reduce the risk of subsequent genital infection with HSV-1.[9 10] Ethnic differences in oral sex practices leading to exposure to oropharyngeal HSV-1 have also been proposed.[11] Assortative (like with like) sexual mixing within ethnic groups may contribute to maintain the difference.[12] Results demonstrated also that HSV type specific serology can improve diagnostic accuracy in a setting where most genital infections are due to HSV-2. The use of type specific serology in GUM settings with a high prevalence of genital herpes due to HSV-1 remains to be validated in clinical studies.

CONTRIBUTORS

AMG, study design, laboratory work, data analysis, and manuscript preparation; MR, MS, laboratory work; CM and MT-F, collection of samples and demographic and clinical data; CS, statistical analysis; all authors reviewed and approved the manuscript.

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